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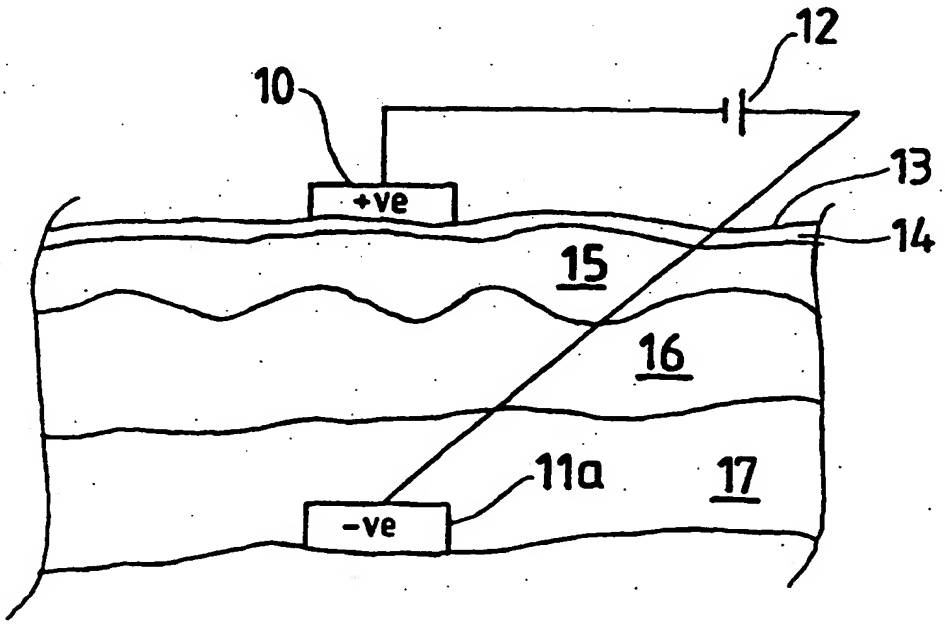
(54) Title: IONTOPHORESIS METHOD AND APPARATUS

(57) Abstract

An iontophoresis method for delivering an active substance or drug to a target tissue which includes the step of sandwiching the target tissue between a donor electrode and receptor electrode which are each electrically connnected to a power source wherein a current path between the donor electrode and the receptor electrode is maintained at a minimum value to enhance delivery of the active substance to the target tissue.



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TITLE

"IONTOPHORESIS METHOD AND APPARATUS"

FIELD OF THE INVENTION

THIS INVENTION relates to the process of iontophoresis whereby the delivery of topical active agents is enhanced by the application of an electrical potential difference.

Iontophoresis targets active agents to tissues underlying the skin such as the dermis, subcutaneous tissue, fascia or muscle, bypassing the gastrointestinal tract as a site of absorption and hence avoiding first pass degradation of the drug.

BACKGROUND OF THE INVENTION

The skin is the major barrier to the entry of foreign solutes from the environment into the body as well to the loss of heat and moisture from the body. The outermost layer of the epidermis, the stratum corneum, is normally assumed to be the major barrier to drug absorption through the skin. It has also been assumed that the drugs penetrating the epidermis are then removed by the dermal blood supply.

Drugs will not penetrate into deeper tissues after topical application if the stratum corneum barrier is not overcome. Complete removal of this barrier should yield tissue levels equivalent to those observed after dermal application. Singh *et al.*, (1993) referred to in the list of references hereinafter, observed that iontophoresis also yielded tissue concentrations of lignocaine and salicylic acid *in vivo*, similar to those observed for dermal application.

Iontophoresis is a process which involves the transport of charged substances into body tissue, such as skin, by the passage of an electric current. Transport of solutes by iontophoresis is dependent on many factors, including solute physio chemical factors which includes (ionic charges [Gangarosa *et al.*, 1980; Pikal, 1990; Srinivasan and Higuchi, 1990; Kasting and Keister, 1989; Phipps *et al.*, 1989; Burnette and Ongpipattanakul, 1987; DeNuzzio and Berner,

1990], the presence of extraneous ions [Bellatone *et al.*, 1986], pH of the donor solution [Siddiqui *et al.*, 1985b and 1989; Burnette and Marrero, 1986; Wearley *et al.*, 1989], ionic strength [Lelawongs *et al.*, 100-; Wearley *et al.*, 1989], solute concentration [O'Malley and Oester, 1955; Bellatone *et al.*, 1986; Wearley *et al.*, 1989], buffer constituents, chemical structure of the solute inclusive of conductivity [Siddiqui *et al.*, 1989]); physiological factors (skin region - density of appendages [Roberts *et al.*, 1982; Feldman *et al.*, 1967], age, sex, race, hydration of the skin [Potts *et al.*, 1984], delipidization - ethanol pretreatment [Srinivasan *et al.*, 1989], fluidisation of lipids and permeability of skin [Tregear, 1966; Phipps *et al.*, 1989]) and electrical factors inclusive of current density [Bellatone *et al.*, 1986; DelTerzo *et al.*, 1989], nature of electrodes [Bellatone *et al.*, 1986, Masada *et al.*, 1989], duration of treatment, nature of current [Okabe *et al.*, 1986; Yamamoto and Yamamoto, 1976 and 1978; Chien *et al.*, 1989; Bagniefski and Burnette, 1990; Pikal and Shah, 1991]).

Hitherto there has been described methods and compositions for enhanced skin concentration of iontophoretically delivered active agents. During iontophoresis, charged compounds pass from a reservoir attached to the skin of a person into the tissue underneath. The process is one wherein the rate of delivery is a function of current, active agent concentration and presence of other ions. It is a generally held belief that higher concentrations of active agent, higher levels of current and lower concentrations of other ions result in greater delivery of the active compound. Generally, iontophoretic devices comprise at least two electrodes - both on the surface, an electrical energy source, such as a battery, and at least one reservoir which contains the active agent to be delivered.

Mention can be made to prior art which describes methods and devices involving the internal placement of iontophoretic electrodes into body cavities. Stephen *et al.*, (US Patent 5222936) describe a method and apparatus specifically for the placement of an

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iontophoretic electrode in the form of a tubular catheter into hollow body cavities containing ion-rich physiological fluids, such as the bladder and vagina. The purpose of their invention was to introduce a technique whereby the selection of the active electrode material and drug counterion would be such as to produce ionic species which interact with one another to minimise or reduce the number or water hydrolysis products produced by electrode decay as a result of the iontophoretic process.

Reference can also be made to German Patents 3809814 and 3844518 which describe electrodes designed for implantation into fluid containing hollow body cavities, specifically the bladder, for the local treatment of bladder cancer by iontophoresis. In these specifications, the receptor electrode was enclosed in a type of girdle worn around the lower part of the body and connected to the electrode placed in the bladder. The electrode placed in the bladder comprised a tubular rigid probe having a peripheral wall and opposed rows of delivery apertures in the peripheral wall. The inserted end of the probe was sealed and a conductor passed down the hollow interior of the probe and was connected to a source of current at an outer end.

US Patent 4411648 also refers to electrode placement in the bladder to prevent infection. In this case, both donor and receptor electrodes in the form of rigid metal probes were inserted into the bladder and the surrounding bladder contents were sterilised by the ions generated by the decomposition of the electrode when the current was passed. All of the abovementioned references rely upon the presence of a fluid environment around their donor electrodes for the passage of drug solution or generation of heavy metal ions and were specifically concerned with delivery of the drug solution to the relevant body cavity.

Therefore, in summary, the aforementioned prior art in the case when two electrodes were placed on the skin was primarily

directed at delivery of a topical active agent to the skin surface or tissues underlying the skin or, alternatively, when a probe electrode was inserted into a body cavity, the fundamental objective was to deliver active agent to the body cavity. Often the distance between the two electrodes was unduly long or circuitous and this was relatively disadvantageous when delivering active substance to a particular target tissue. This meant that it was often the case that effective concentrations of active substance were not delivered to the required locations.

SUMMARY OF THE INVENTION

It therefore is an object of the invention to provide iontophoresis apparatus and a method of use which may alleviate these problems.

The invention therefore is specifically concerned at an iontophoresis method which involves "sandwiching" of a particular target tissue between electrodes which provides deeper tissue penetration of active substance than the prior art discussed above. This method achieves a particularly desired objective where the distance between the electrodes is at a minimum which achieves the desired potential difference and thus achieves the required electrical conduction path. In other words, if this technique is followed, there is encountered the least electrical resistance between two electrodes.

The method of the invention therefore includes the step of sandwiching a target tissue requiring delivery of an active substance between a donor electrode and a receptor electrode which are each electrically connected to a power source wherein a current path between the donor electrode and the receptor electrode is maintained at a minimum value to enhance delivery of active substance to the target tissue which may be at a desired concentration.

The donor electrode usually has an active substance or drug associated therewith while the receptor electrode will complete

an electrical circuit when placed adjacent to the receptor electrode.

The iontophoresis method of the invention may also be applied to organs including, but not limited to, the eye, nose, ear, vagina, penis, where the receptor electrode is positioned across the organ, compared to the surface of the organ. The field of the present invention will also include the iontophoresis of drugs into muscle tissue using a needle electrode placed in the deep tissue via acupuncture sites as described hereinafter. This technique differs from that of MENS, the application of therapeutic electrical currents to muscle between electrodes which is used in physiotherapy as the method of the present invention requires the delivery of an active drug substance by the applied current, which is also of a different power and frequency. Thus, normally the current utilised in the iontophoretic apparatus of the invention will be 0.05 - 5.0 milliamp/sq cm.

Examples of drugs or therapeutic substances that may be used as an active agent in the apparatus of the invention include non-steroidal anti-inflammatory agents (NSAIDS) which, when taken orally, may cause irritation of the stomach or intestine, permeation enhancers, buffers, baceriostatics, antioxidants, anaesthetics, hormones, anti-arthritics, anti-virals, antineoplasics, anti-inflammatories, muscle relaxants, antihistamines, antibiotics, and corticosteroids.

Specific examples of antibiotics include clindamycin, spectromycin and vancomycin. Specific examples of suitable corticosteroids include hydrocortisone and dexamethasone.

The active agent may also include any biologically active compounds or mixture of compounds that have therapeutic, prophylactic, pharmacological, physiological effect on a subject and may also include one compound or mixture of compounds that produce more than one of these effects.

Vehicles or excipients which may be used in the apparatus of the invention include any non-toxic aqueous compound

which is suitable for topical application and which are liquid at room temperature.

The type of electrodes utilised in the method of the invention may vary dependent upon the required application. If the donor electrode is to be applied topically, then such electrode will most commonly be in the form of a pad containing an active substance in solution having a backing metal plate or electrode. An example of such an electrode is the conventional gel type pad (such as IOMED). The donor electrode is usually placed on an outer body surface, such as skin, while the receptor electrode is an inserted electrode which may be a probe electrode suitably of the type hereinafter described or a needle electrode which is inserted directly into tissue. The use of a needle electrode as receptor electrode provides a distinct advantage over the probe type electrodes discussed above in that the probe type electrodes can only be inserted in body orifices or cavities and thus have only a limited application. In contrast, the needle electrode can be utilised or inserted directly into tissue and can also be inserted into body orifices and cavities.

The needle electrode utilised in the iontophoresis method of the invention may include a needle part having an outer end which is preferably pointed in the same manner as a syringe needle. The needle part may also include an insulating sheath adjacent to the outer end. The needle electrode may also include an electrode body made of any suitable metal such as platinum, silver or stainless steel. A conductor or wire may pass through the electrode body and thus current may travel along the wire and continue along the needle. The wire may be connected to a source of electrical current.

It will also be appreciated that the term "topical" as used herein covers administration to the mouth, penis, nose, eye, ear, vagina, anus or any other body part accessible to local administration.

It will be found in practice that operation of the method of the invention especially when utilising the needle electrode may be

used to target any tissue area included in the epidermis, dermis, subcutaneous tissue, fascia, muscle, fat pad, deep muscle, joints, bones, nerves, eyes, blood or lymphatic systems. The administration of an active compound in accordance with the method of the invention travels to the target site or tissue more quickly than by oral administration and in higher concentrations. The method of the invention may be used in relation to treatment of arthritis, sciatica and rheumatism. Another advantage of active agent administration using the method of the invention is essentially a localised application that will alleviate chronic pain.

In a preferred embodiment of the invention, the method of the invention may be utilised delivery of an active substance of the type described above to locations such as the ear, nose or throat. The donor electrode, in this aspect of the invention, is an insertable probe electrode including an elongate probe body having an insert end including a compartment for containing the drug or active substance.

Suitably the compartment comprises a hollow space adjacent the insert end which is provided with access means for drug delivery. The access means may include a plurality of perforations or drug delivery apertures or alternatively, a porous sheath or sleeve such as a dialysis membrane. The donor electrode may also include an insulating handle.

The donor electrode, in another embodiment, may include a detachable sheath including a number of perforations or drug delivery apertures at one end. The compartment may be formed when the sheath is attached to the probe body.

The probe body may be solid as shown but the compartment may replace all of the probe body if desired and thus terminate adjacent the insulating handle if required.

In another embodiment, the probe body may be flexible instead of rigid. Any suitable flexible material may be utilised such as elastomeric material such as synthetic or natural rubber or resilient

plastics material. This is in contrast to the previously described embodiment where the probe body may be formed from rigid plastics material such as polycarbonate or polyethylene. Again, as in the previously described embodiment, the compartment may terminate adjacent the insulating handle if desired.

In another embodiment, the tip of the electrode may comprise a dialysis membrane if the electrode has to contact damaged, inflamed or sensitive tissue.

In the specific embodiment of delivery to the ear, nose or throat as described above, a probe electrode of the type described above may be inserted into the nasal sinus where the insert end is in contact with tissue adjacent the eye as shown. The receptor electrode may be in bearing contact with a part of the eye as shown (e.g. eyelids, eyebrows, conjunctiva).

It will be appreciated in this embodiment that the donor electrode may be inserted into an ear cavity in substitution of a sinus cavity if desired.

It will also be appreciated in this embodiment that the receptor electrode may be a conventional electrode plate or pad as described above in regard to the first aspect of the invention.

It will also be appreciated that the method of the invention may also include the use of probe electrodes of the type discussed above which may be inserted into body cavities that may be adjacent or substantially parallel to each other such as the nasal cavity and eustachian tube, trachea and oesophagus or rectum and urethra. It is also possible in regard to operation of the method of the invention that a needle electrode may be utilised in combination with a probe electrode.

In another aspect of the invention, there may be provided iontophoresis apparatus that may be utilised in regard to use of the method of the invention. Such apparatus may include a needle electrode as described above or a probe electrode as described above.

BRIEF DESCRIPTION OF THE DRAWINGS

Reference may now be made to a preferred form of the invention as shown in the attached drawings, wherein:-

FIG. 1A is a schematic drawing illustrating a conventional iontophoresis method where the two electrodes are placed adjacent each other on a skin surface as described above;

FIG. 1B is a schematic drawing illustrating the iontophoresis method of the invention;

FIG. 1C is a drawing illustrating the application of the method of the invention to deep muscle delivery;

FIG. 1D represents a schematic form of a needle electrode for use in the method of the invention;

FIG. 1E represents a side view of the embodiment of the invention to delivering active substance to the ear, nose or throat;

FIG. 1F represents a front view of the embodiment shown in FIG. 1E;

FIGS. 2A, 2B, 2C, 2D, 2E and 2F illustrate various forms of needle electrodes for use in the method of the invention;

FIGS. 3A, 3B and 3C illustrate various forms of placement of electrodes in the method of the invention;

FIGS. 4A, 4B and 4C illustrate various forms of probe electrodes for use with the present invention;

FIG. 5 represents a specific form of probe electrode for use with the present invention; and

FIGS. 6 and 7 compare the method of "sandwich" placement of electrodes in accordance with the method of the invention compared to conventional placement of electrodes as described in more detail in the EXPERIMENTAL SECTION.

DETAILED DESCRIPTION

In FIG. 1A, there is shown a conventional method of iontophoresis delivery wherein electrodes 10 and 11 are electrically connected to battery 12. Each electrode 10 and 11 is applied to skin

surface 13 and there is also shown epidermis layer 14, dermis layer 15, subcutaneous fat layer 16, muscle layer 17 and deep tissue layer 18.

In FIG. 1B, in contrast, the electrodes 10 and 11a have been placed so that a layer of tissue is interposed or sandwiched therebetween in accordance with the invention whereby delivery of active substance in accordance with the required concentration may be facilitated to the target tissue. Electrode 11a is a needle electrode.

In FIG. 1C, there is shown an application of the method of the invention for delivery of active substance in the required concentration to deep muscle layer 18. There is also utilised an electrode 10 in the form of a skin pad containing a drug to be delivered to deep muscle layer 18 as well as needle electrode 11a.

In FIG. 1D, there is shown needle electrode 11a including insulated wire 19, electrode body 20, insulating sheath 21 and needle tip 22. The insulated wire is electrically connected to a source of electrical power (not shown) and the donor electrode (not shown). The needle electrode is shown inserted into a tissue layer 23 through skin surface 13.

In FIG. 1E, there is shown an embodiment of the iontophoretic method of the invention as applied to delivery of a drug to the ear, nose or throat or ophthalmic delivery. Again, there is utilised skin pad electrode 10 and needle electrode 11a. Electrode 10 is applied to the eye and electrode 11a is inserted in the nasal sinus passage. The path of the current is shown by the line 24 in phantom.

In FIG. 1F, there is shown three alternative positions for electrode 10 which may occur on the eye, adjacent the ear, or above the ear as shown by the various locations designated 11a. There is also shown the current path 24a and 24b which are applicable.

In FIGS. 2A through 2F, there are shown various kinds of needle electrodes that may be used in the iontophoretic method of the invention.

FIG. 2A shows two types of needle 25 and electrode body 26. FIG. 2B illustrates an ovoid body, FIG. 2C illustrates a curved body, FIG. 2D illustrates a hollow loop body, FIG. 2E illustrates a body 26 provided with a hook 27 and FIG. 2F shows a flat filled loop body.

FIGS. 3A through 3C illustrate the possible combinations of placement positions for donor and receptor electrodes for direct tissue delivery in accordance with the method of the invention.

In FIG. 3A, there is shown a situation where both electrodes 27 and 28 penetrate target tissue 29. Electrodes 27 and 28 may be either the donor or receptor electrode. Target tissue 29 may include any particular tissue, organ, tumour, injured, infected or diseased site within or outside the body.

In FIG. 3B, electrode 27 is located outside target tissue 27 and one electrode 28 penetrates target tissue 27.

In FIG. 3C, both electrodes 27 and 28 are located adjacent to target tissue 29.

In each of the cases shown in FIGS. 3A through 3C, electrodes 27 and 28 may comprise a needle electrode, static probe, micro dialysis tubing or probe, conventional surface electrode, any surgically implanted electrode or conducting material introduced into the tissue on its surface or on the outside of the body.

In FIGS. 4A through 4E, there are shown various kinds of rigid probe electrodes for use with the method of the invention.

In FIG. 4A, there is shown probe 30 having insulating handle 31, conductor or electrode 32 which is connected to a power source (not shown), insulation 32a, probe body 33 and compartment 34 for containing a drug solution which may emerge from holes or perforations 35 on compartment 34 when current is applied.

FIG. 4B shows a similar probe electrode to that shown in FIG. 4A with the exception that compartment 34 is longer and confined to one side of the body 33.

FIG. 4C shows a similar probe electrode to FIG. 4A with the exception that compartment 34 is longer when compared to compartment 34 in FIG. 4A.

FIG. 4D shows a detachable sheath 36 having a tip 37 and holes 35 and resilient tube or sleeve 38 which is adapted to fit over probe body 39 shown in FIG. 4E which has electrode 32 associated therewith as well as insulating handle 31. Electrode 32 has end 32b which extends beyond body 33 as shown and into sheath 36 to provide compartment 34.

It will also be appreciated that probe body 33 may be flexible or resilient if desired or alternatively, may be made from rigid material. The compartment 34 may be made as long as may be desired and may even extend to the insulating handle 31 if required.

In FIG. 5, there is shown another type of probe electrode 40 which is provided with a dialysis membrane 41 if desired which covers compartment 34. The probe electrode 40 may have a flexible or rigid body or casing 33. The dialysis membrane may be from 1-3 cm long and may be modified for one-sided delivery as shown in FIG. 4B or both sides as shown in FIG. 4C.

EXPERIMENTAL SECTION

Chemicals and Instruments:

[^{14}C]Lignocaine HCl (specific activity 48 mCi/mmol, purity > 97%) and [^{3}H]Ethanolamine (specific gravity 35 mCi/mmol) were purchased from either New England Nuclear, c/- DuPont (Australia) Ltd., Sydney or Amersham Australia Pty. Ltd., Sydney. Tissue solubiliser, NCSII, and liquid scintillation cocktails (OCS and Emulsifier-Safe) were purchased from Amersham Australia Pty. Ltd., Sydney. HEPES (N-2-hydroxyethylpiperazine-N-2-ethanesulphonic acid) buffer salt was purchased from Sigma Australia, Sydney and all other chemical reagents were of analytical grade. A liquid scintillation counter (Tri-carb^{R} 4000 series, United Technologies Packard, USA) was used to determine the radioactivity in the samples. The constant

current used in the experiments was generated by a custom-made constant-current source.

Animals:

Male Wistar rats (300-350 g) were used in the studies. The animals were housed under standard laboratory conditions (20.0 ± 0.5°C, relative humidity 55-75%) and supplied with a normal pellet diet and water *ad libitum*. All experiments had previously been approved by the Animal Experimentation Committee of the University of Queensland.

In Vivo Epidermal Penetration and Local Tissue Uptake Studies:

The rats were lightly anaesthetised with sodium pentobarbitone (60 mg/kg *i.p.*) or ketamine (130.5 mg/kg)/azaperone (75 mg/kg) mixture and their body temperature was maintained throughout the experiment at 37°C by placing them on a heating pad. The hair on the dorsal area was clipped with electrical clippers, and any residual hair was removed by application of a depilatory cream (Singh & Roberts, 1993) [Nair; Carter-Wallace (Australia) Pty. Ltd.). The depilatory area was swabbed with a mixture of distilled and deionised water and methyl alcohol (Singh & Roberts, 1993) to remove any traces of the depilatory. A donor glass absorption cell (internal diameter, 1.8 cm) was fixed to the epidermis using adhesive. The glass cell was warmed to 37°C by means of an external heating device (Siddiqui *et al.*, 1985). A 2 ml solution of 50 mM HEPES buffer, pH 6.3 spiked with [^{14}C]lignocaine and [^{3}H]ethanolamine was placed in the donor solution. The solution was stirred by a glass stirrer driven by an external motor. A silver electrode (anode) was placed in the donor cell and the circuit completed by placement of a receptor electrode as described later. A current of 0.38 mA/cm^2 was applied between the two electrodes. Samples (10 μl) were removed from the donor cell at 0,15,30,45,60,90,120 min and placed in scintillation vials. The glass cell was removed from the rat skin at 2 hr after commencement of the experiment, and the application area

was wiped dry with blotting paper. A blood sample was then taken from the heart, and the animals sacrificed with overdose anaesthetic ether. Immediately thereafter the tissues below the treated with, i.e., skin, subcutaneous tissue, muscle lining or superficial muscle, muscle and fat pad were removed by dissection and placed in preweighted scintillation vials (Singh & Roberts, 1993). Similarly, the tissues below the contralateral side were also removed. Dissection instruments were cleaned with alcohol soaked swabs between each tissue sample to prevent cross contamination of radiation. Epidermal and dermal layers were separated by exposure to concentrated ammonia fumes following the method of Kligman and Christophers (1963).

Receptor Electrode Placement

Part A:

A dermal absorption cell was affixed to the skin of the rat, 7 cm or directly adjacent to the donor cell. A solution of 2 mL 20 mM HEPES was placed in this receptor cell and the circuit completed.

Part B:

While the rat was anaesthetized, an incision was made on the abdomen of the rat. An IOMED^R receptor was inserted into the abdomen, against the abdominal muscle layer directly beneath the donor electrode site. Parafilm^R was placed on the rats organ to provide protection from the receptor. The rat abdomen was then sutured, and the rat tested 1 hr to allow the blood supply to stabilise before commencement of iontophoresis.

Sample Treatment:

Aqueous samples removed from the glass cell were directly mixed with 5 ml of liquid scintillation cocktail Emulsifier-Safe and counted on liquid scintillation counter. The tissue samples were solubilised with 1 ml of tissue solubiliser NCSII at 50°C for 6-8 hrs, longer where required, prior to the addition of 10 ml of organic scintillant OCS for scintillation counting.

Analysis:

Zero-time samples from the cell were used to represent the initial solution concentration, and radioactivity in the tissues and plasma were converted to a fraction of the initial solution concentration (concentration fraction).

Results and Discussion

FIGS. 6 and 7 compares the "sandwich" placement of electrodes with conventional placement of electrodes, that is, side-by-side, on the surface of the skin, of lignocaine and ethanolamine, respectively.

When electrodes are placed adjacent to each other on the skin of a subject, the path of solutes follows that of least resistance, that is, through the dermis. However, when electrodes are placed in this "sandwich" form, a higher concentration of solute ions in deeper tissues directly beneath the electrode is observed.

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LEGENDS

FIG. 7

Penetration of 3H ethanolamine into tissue. Comparison of receptor placement.

—□— treated tissue - cells positioned "sandwich" style

····◇···· contralateral tissue - cells positioned "sandwich" style

---○--- treated tissue - cells positioned adjacently on surface of skin

---△--- contralateral tissue - cells positioned adjacently on surface of skin

FIG. 8

Penetration of 14C lignocaine into tissue. Comparison of receptor placement.

—□— treated tissue - cells positioned "sandwich" style

····◇···· contralateral tissue - cells positioned "sandwich" style

---○--- treated tissue - cells positioned adjacently on surface of skin

---△--- contralateral tissue - cells positioned adjacently on surface of skin

CLAIMS

1. An iontophoresis method for delivering an active substance or drug to a target tissue which includes the step of sandwiching the target tissue between a donor electrode and receptor electrode which are each electrically connected to a power source wherein a current path between the donor electrode and the receptor electrode is maintained at a minimum value to enhance delivery of the active substance to the target tissue.

2. An iontophoresis method as claimed in Claim 1 wherein the donor electrode is a needle electrode inserted into the target tissue.

3. An iontophoresis method as claimed in Claim 1 wherein the donor electrode is a probe electrode inserted into the body cavity.

4. An iontophoresis method as claimed in Claim 1 wherein the receptor electrode is a pad for topical application.

5. An iontophoresis method as claimed in Claim 1 for delivery to the active substance to the ear, nose or throat wherein a probe or needle electrode which functions as the donor electrode is inserted in a sinus cavity and a receptor electrode in the form of a pad is applied to an eye, an ear or location adjacent the ear.

6. Iontophoresis apparatus for carrying out the method of Claim 1 wherein the donor electrode is a needle electrode or probe electrode.

7. Iontophoresis apparatus as claimed in Claim 6 wherein the needle electrode includes an electrode body, a conductor passing through the electrode body and a needle part electrically connected to the conductor.

8. Iontophoresis apparatus as claimed in Claim 7 wherein the needle electrode includes an insulating handle.

9. Iontophoresis apparatus as claimed in Claim 7 wherein there is also provided an insulating sheath located adjacent said needle part or the electrode body.

10. Iontophoresis apparatus as claimed in Claim 6 wherein the probe electrode includes an electrode body, a conductor passing through the electrode body and a compartment for storage of active substance located adjacent an outer end of the body wherein said compartment is provided with access means whereby active substance can be delivered to adjacent tissue.

11. Iontophoresis apparatus as claimed in Claim 10 wherein the access means includes apertures in an external wall of the compartment.

12. Iontophoresis apparatus as claimed in Claim 10 wherein the access means includes a dialysis membrane or porous membrane adjacent to the compartment.

13. Iontophoresis apparatus as claimed in Claim 10 wherein there is also provided a detachable sheath having said access means which is adapted for engagement with said electrode body.

14. Iontophoresis apparatus as claimed in Claim 13 wherein the electrode body has an outwardly extending conductor part adjacent an outer end of the electrode body.

15. A needle electrode for use in iontophoresis comprising an electrode body, a conductor passing through the electrode body, a compartment for storage of active substance and a needle electrically connected to the conductor.

16. A needle electrode as claimed in Claim 15 including an insulating sheath on the electrode body adjacent the needle.

17. A needle electrode as claimed in Claim 15 also including an insulating handle.

18. A probe electrode for use in iontophoresis including an electrode body, a conductor passing through the electrode body and a compartment for storage of active substance located adjacent an outer end of the body wherein said compartment is provided with access means whereby active substance can be delivered to adjacent tissue.

19. A probe electrode as claimed in Claim 18 wherein the access means includes apertures in an external wall of the compartment.

20. A probe electrode as claimed in Claim 18 wherein the access means includes a dialysis membrane or porous membrane adjacent to the compartment.

21. A probe electrode as claimed in Claim 18 wherein there is also provided a detachable sheath having said access means which is adapted for engagement with said electrode body.

22. A probe electrode as claimed in Claim 21 wherein the electrode body has an outwardly extending conductor part adjacent an outer end of the electrode body.

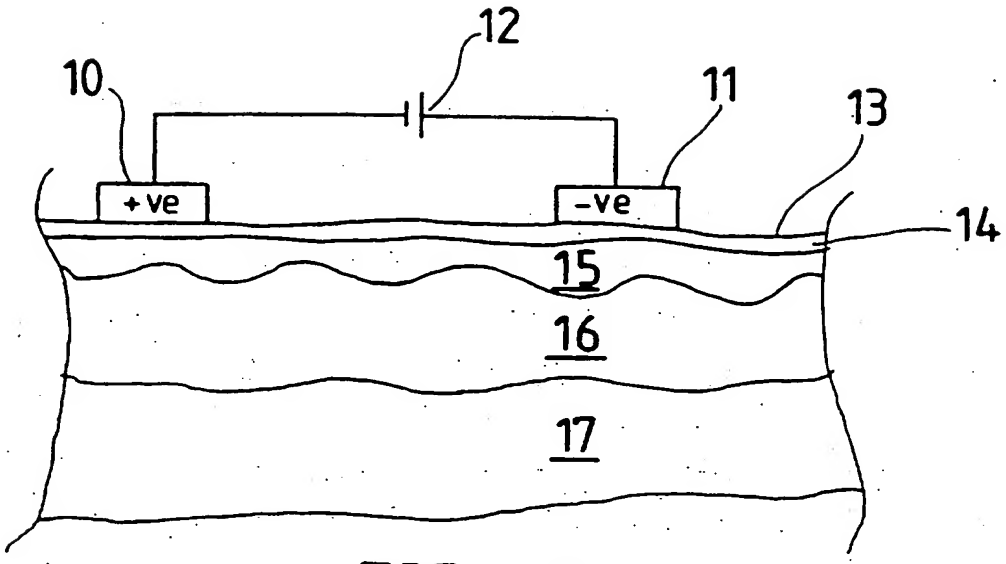

FIG. 1A

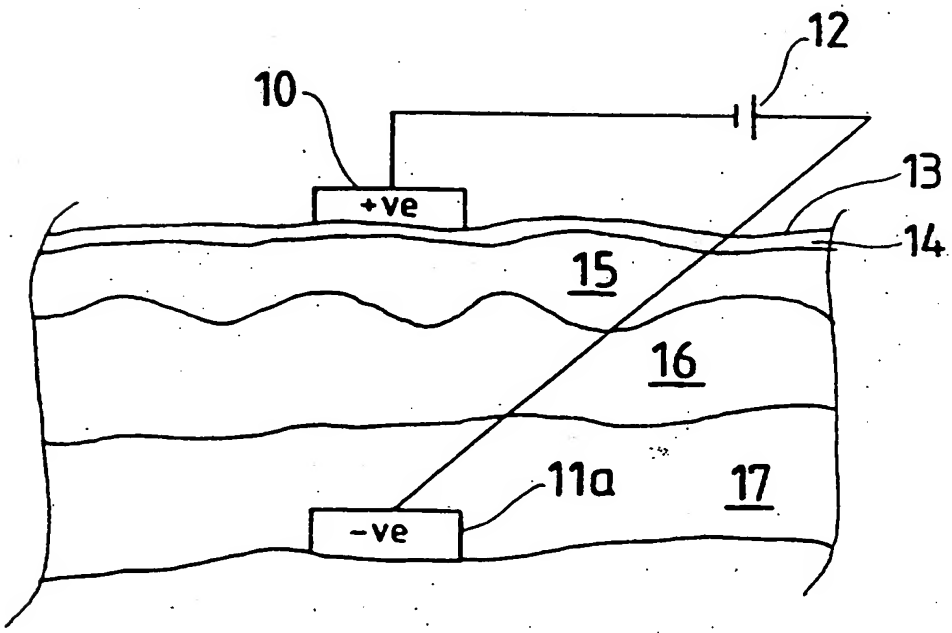

FIG. 1B

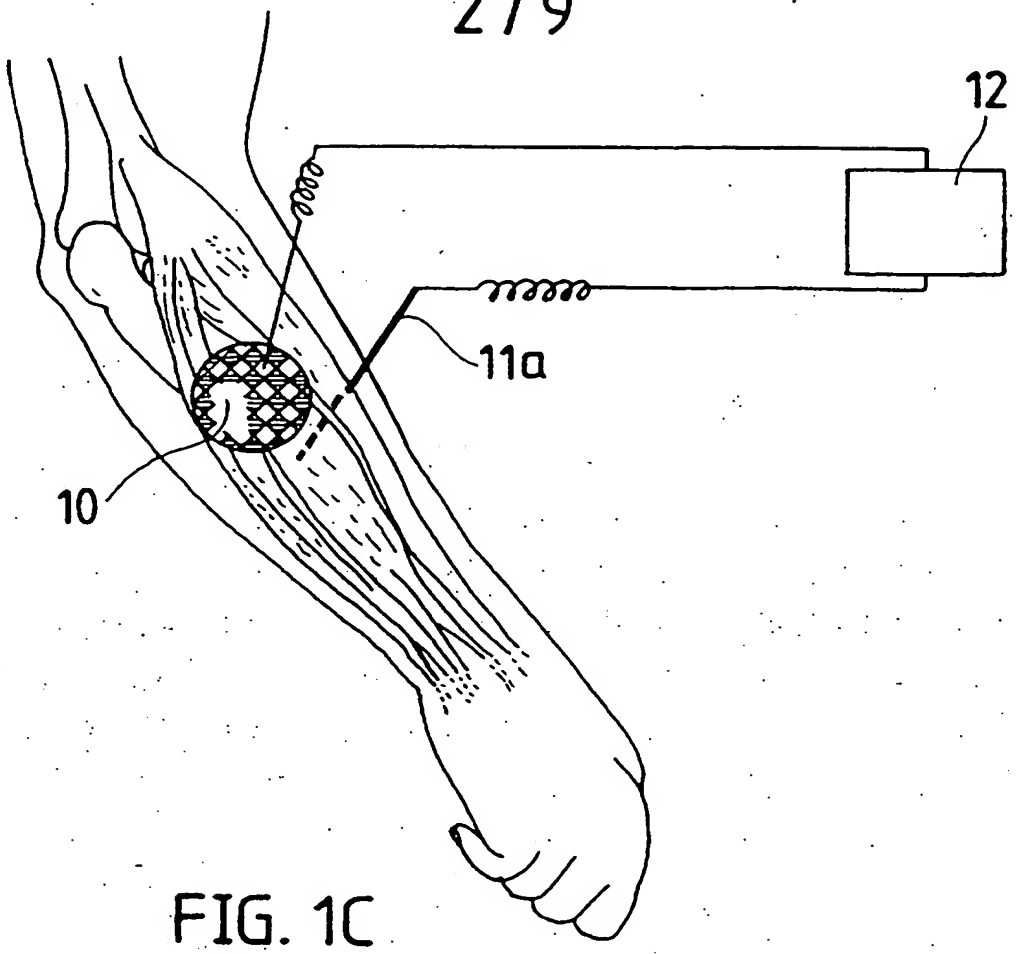

FIG. 1C

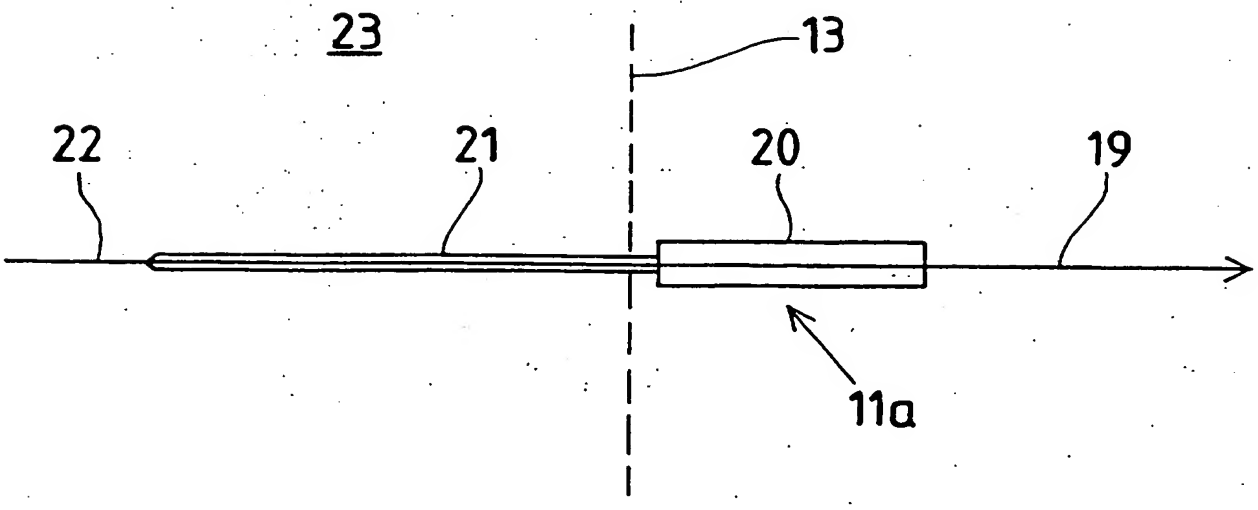

FIG. 1D

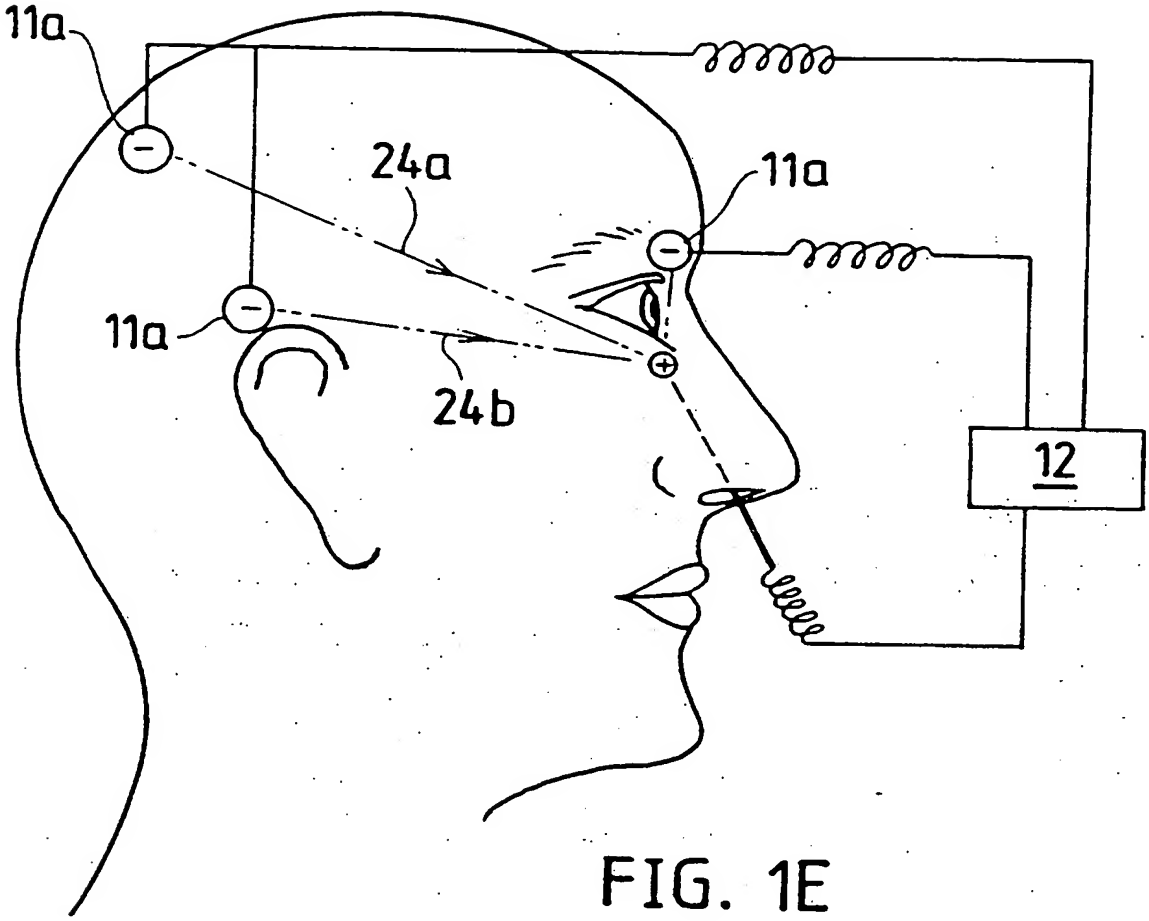

FIG. 1E

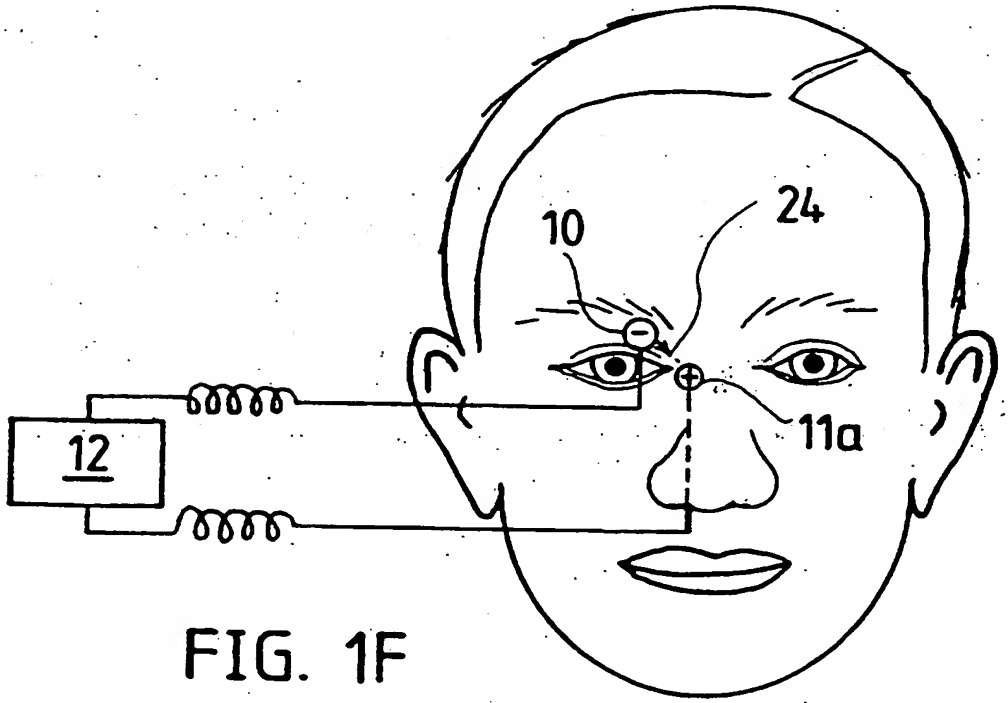

FIG. 1F

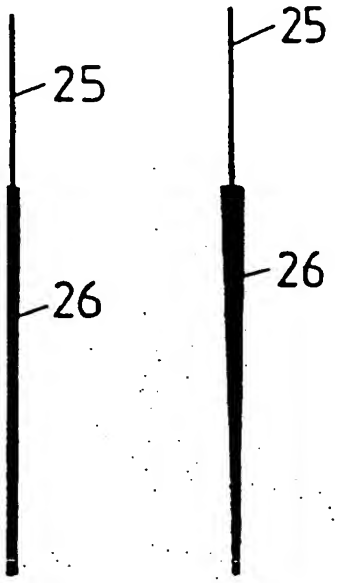

FIG. 2A

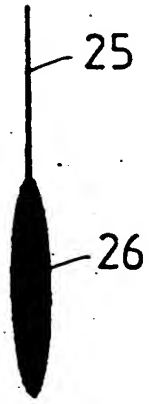

FIG. 2B

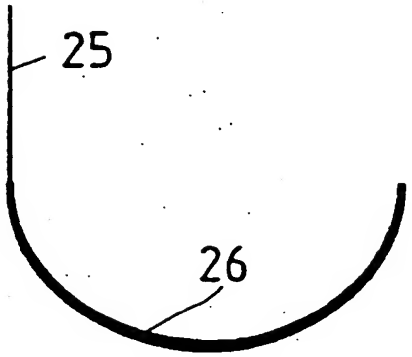

FIG. 2C

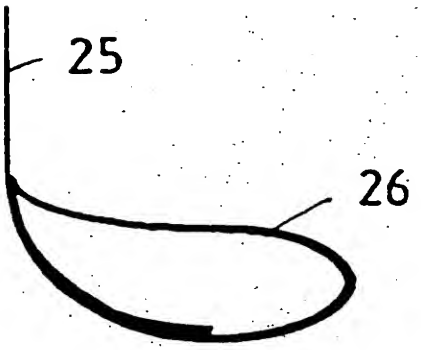

FIG. 2D

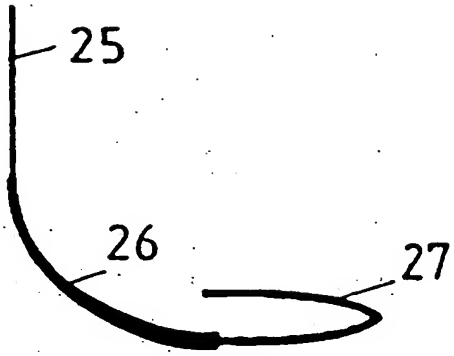

FIG. 2E

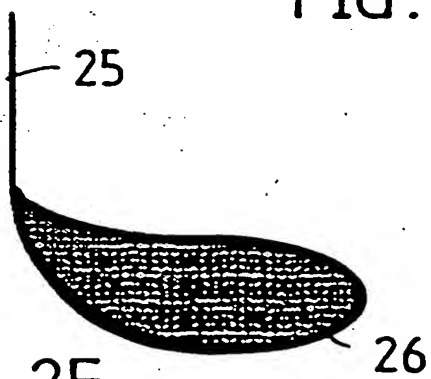

FIG. 2F

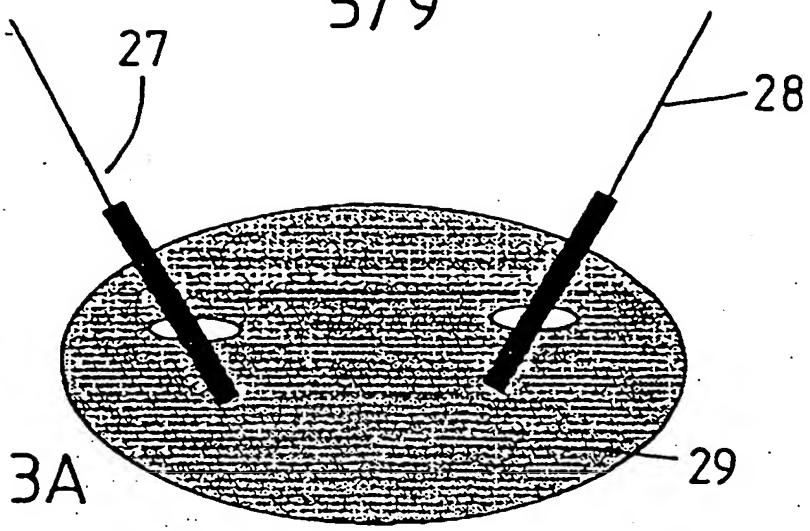

FIG. 3A

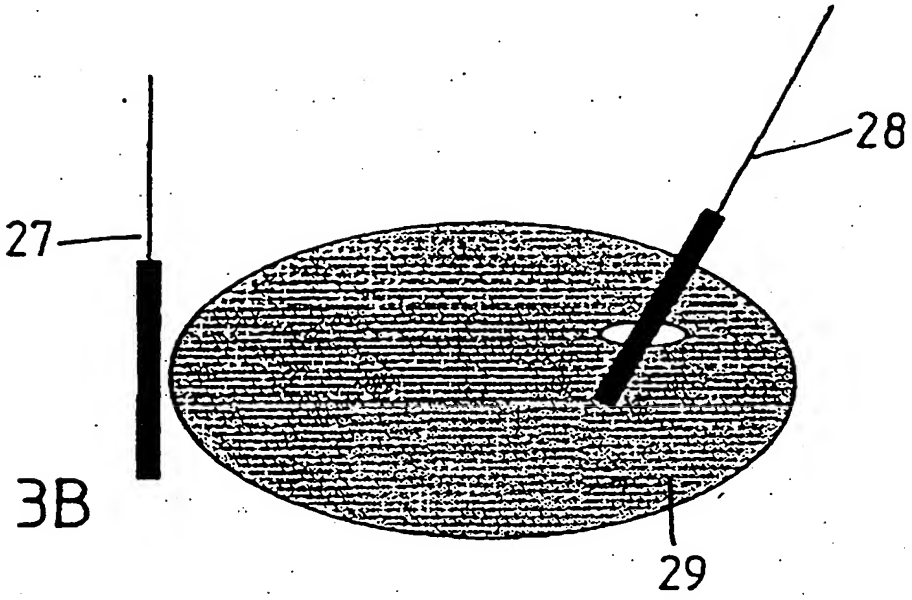

FIG. 3B

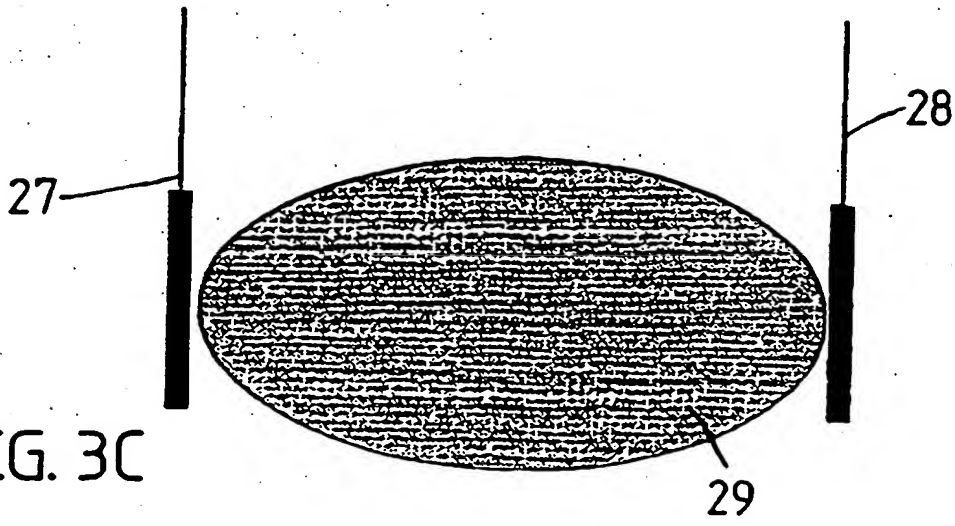

FIG. 3C

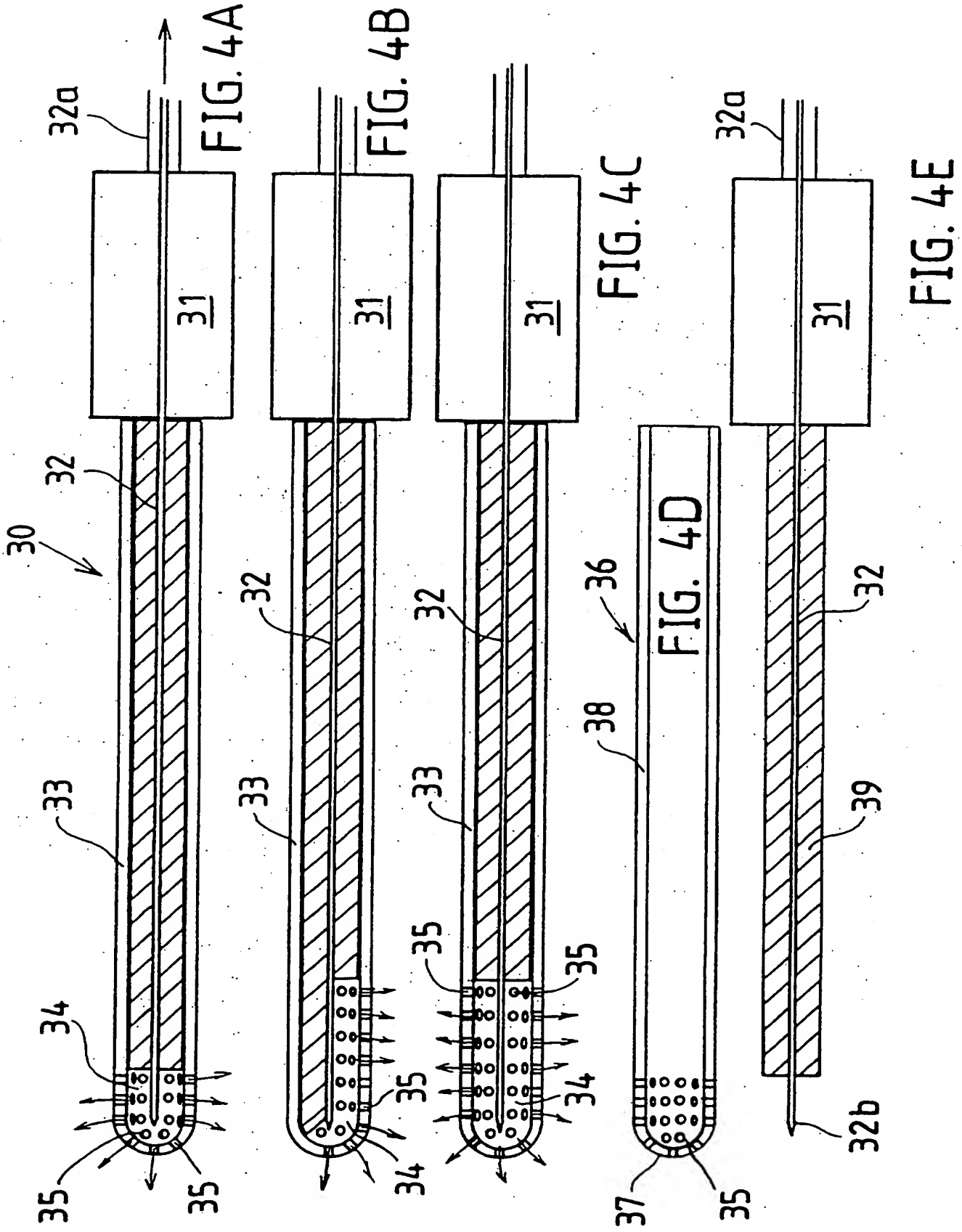
FIG. 4A
FIG. 4B
FIG. 4C
FIG. 4D
FIG. 4E
30
31
32
32a
32b
33
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35
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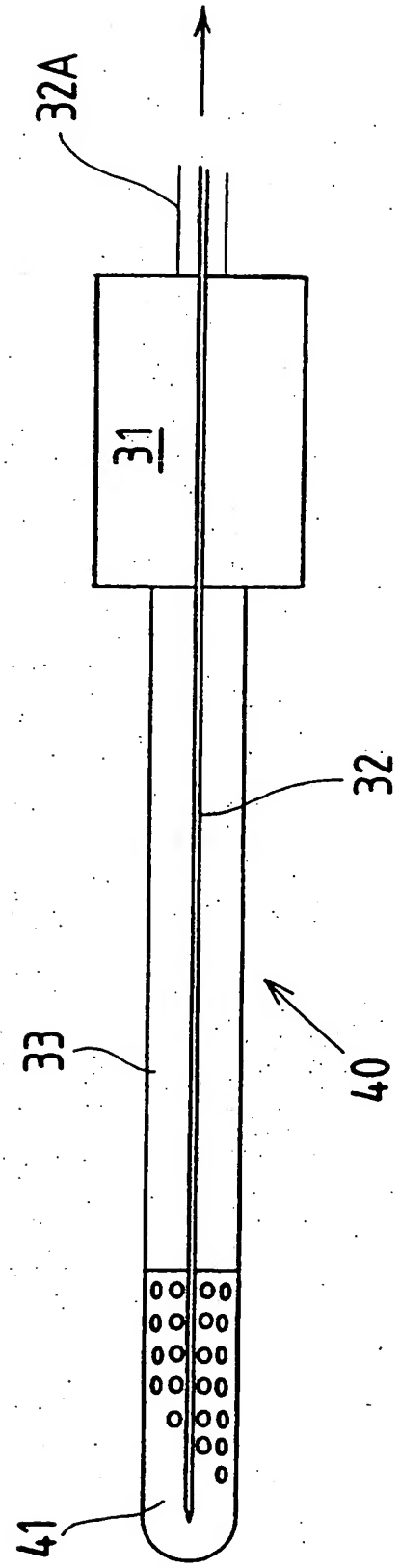

FIG. 5

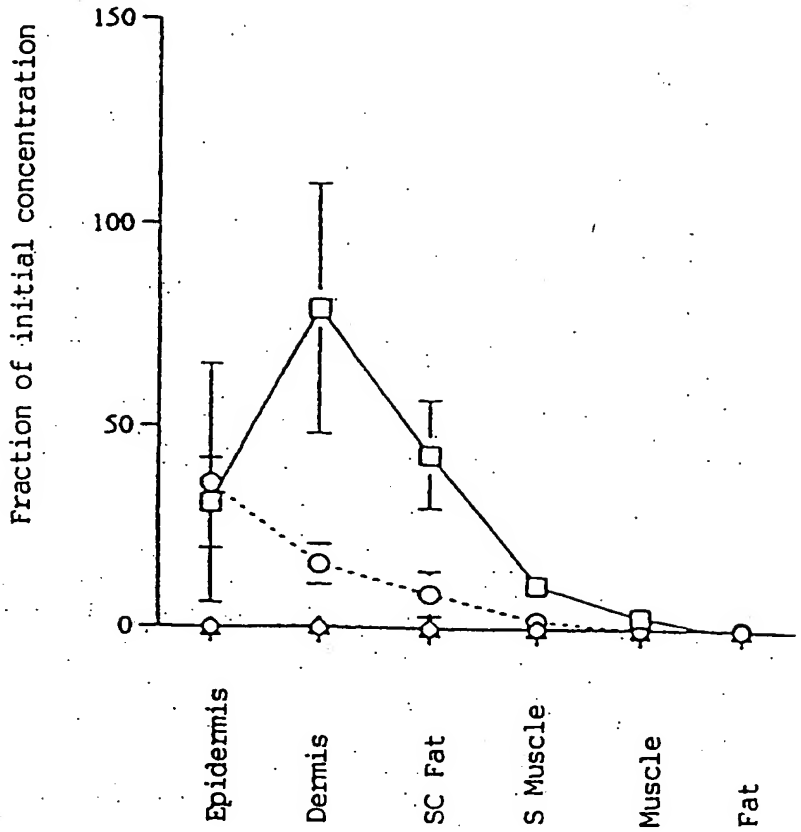
Fraction of initial concentration
150
100
50
0
Epidermis
Dermis
SC Fat
S Muscle
Muscle
Fat

FIG. 6

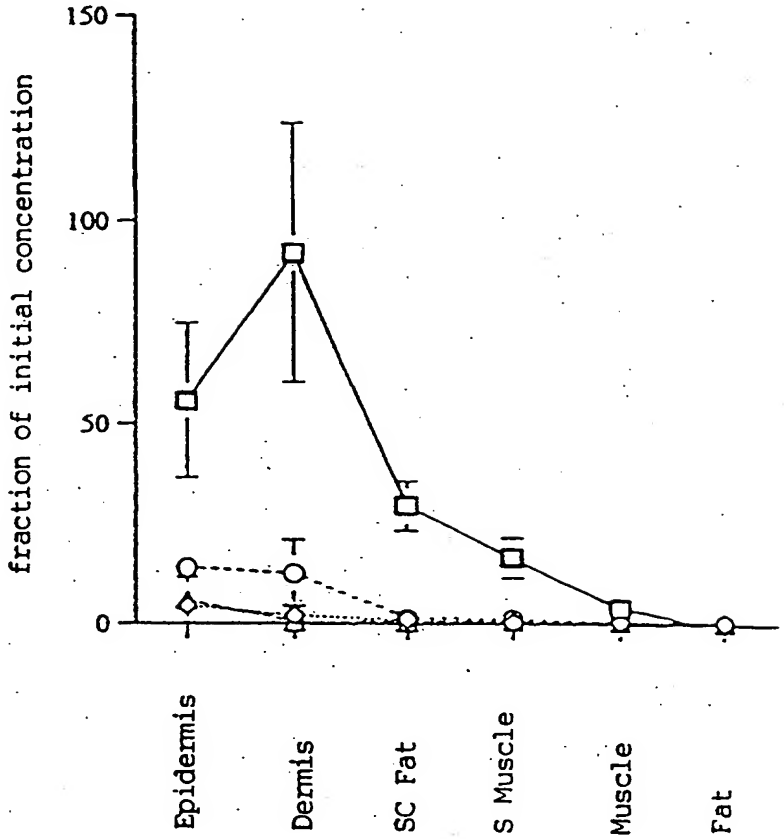
150
100
50
0
fraction of initial concentration
Epidermis
Dermis
SC Fat
S Muscle
Muscle
Fat

FIG. 7

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 95/00816

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61N 1/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC : (as above)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU : IPC (as above)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Dialog One Search (Iontophorisis: Needle or probe)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94/05369 (Cortrak Medical, Inc.) 17 March 1994 Whole document	1,3,4,6,10-13,18-21
X	WO 94/05361 (Cortrak Medical, Inc.) 17 March 1994 Whole document	18-20
X	US 5174304 (Latina et al) 29 December 1992 Abstract, figures, Col. 1 & 2	1,18

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
23 January 1996

Date of mailing of the international search report
12 FEB 1996

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 95/00816

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 510 857 (British Technology Group) 28 October 1992, Columns 1 to 3	1,18
X	EP 438 078 (Rossi et al) 24 July 1991 Columns 1 to 3	18-20 11,12
X	WO 91/16945 (Feiring) 14 November 1991 Pages 5 to 7, figure 3, 3A	18-20
X	US 5 002 956 (Thiel) 26 March 1991 Abstract	1,3,18
X Y	EP 378 132 (Justribo et al) 18 July 1990 Claim 4, figure 3	15,16 2,6,7,9
X	FR 2 516 388 (Carne) 20 May 1983 Abstract, figures	2,6,7,9,15,1
X Y	US 3 991 755 (Vernon et al) 16 November 1976 Whole document	1,18 5

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/AU 95/00816

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	9405369	US	5286254	EP	611311	JP	7500523
		WO	9405361	US	5282785	US	5458568
WO	9405361	US	5286254	EP	611311	JP	7500523
		WO	9405369	US	5282785	US	5458568
US	5174304	CA	2051392	US	5025811	WO	9112049
EP	510857	CA	2051392	US	5025811	WO	9112049
EP	510857	GB	2255020	JP	5115563		
EP	438078	AU	69243/91	BR	9100100	CA	2033833
		IT	9040007	IT	1239088	JP	4212379
		PT	96474				
WO	9116945	AU	79010/91	CA	2081666	EP	527920
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US	5002956	AT	84715	CA	1331567	DE	3809814
		EP	334243	ES	2053839	DE	3844518
EP	378132	ES	2012944				
FR	2516388	NONE					
US	3991755	NONE					

END OF ANNEX